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Single- and/or double-membrane viral factories?

Editorial

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Once entering the cell host, viruses needs to interact with intracellular membranes in order to build up their replication organelles or factories, resulting in a remodeling of the cell membranes, the hallmark of virus infection.

Positive (+) strand RNA viruses represent the largest group of RNA viruses. Among them two different architectures of replication factories (morphotypes) have been described so far, differing mainly in the amount of lipid bilayers they have: one or two [1].

The **single membrane** morphotype consists in the formation of negatively curved membranes or invaginations towards the lumen of the host organelle, resulting in the formation of vesicles, vacuoles or spherules. This strategy is used by members of the families *Nodaviridae, Bromoviridae, Togaviridae* and *Flaviviridae*.

The **double-membrane** morphotype involves the formation of membranes with positive polarity generating vesicles or tubules containing two membranes. These double-sealed structures have been associated with infections of members of the families *Coronaviridae, Arteriviridae, Picornaviridae, Caliciviridae, Closteroviridae* and *Flaviviridae*.

To our current knowledge the only (+) strand RNA family following both strategies is the family *Flaviviridae*. It seems, however, that members of the same genus within this family follow the same strategy. Thus, members of the genus *Flavivirus* induce the formation of vesicles at the endoplasmic reticulum (ER), while hepatitis C virus (HCV) –belonging to the genus *Hepacivirus*- induces the formation of double membrane vesicles (DMVs) that remain connected to their cell source, also ER, through neck-like structures. This family comprises two more genera: *Pestivirus* and *Pegivirus*, from which it still remains to be elucidated how their members remodel the cell membranes upon infection.

The formation of membrane invaginations in the host organelles is normally associated with the presence of a pore or opening towards the cytosol, making these organelles as the suitable viral factories for the synthesis of new RNA [2-5]. Indeed the presence of these pores ensures their active role in replication, allowing a flow of nucleotides and newly synthesized RNA, whereas the invagination provides a protected environment, where the RNA can be replicated/stored, while being hidden from the threatening activity of nucleases or the pattern recognition receptors.

However the functionality behind the induction of double-layered structures remains to be determined. Protection from cell sensors is already achieved with only a single membrane. Thus, there must be another reason for the formation of these structures containing two membranes.

The absence of an –so far unknown- opening connecting their lumen to the cytosol makes it hard to understand how these structures could play a role in replication. One explanation would be that these openings or pores might be beyond the resolution of the so far used methods, like a proteinaceous or a lipid channel and, therefore, remain to be visualized yet. An alternative explanation relates to the biogenesis mechanism of these structures. Thus in picornavirus-infected cells the DMVs are formed from single membrane tubules that undergo secondary invaginations generating the double membraned structures [6,7]. The synthesis of RNA correlates indeed with the formation of the single membrane structures, indicating that the double-membranous structures are likely representing a side effect of the picornaviral-infection. In this fashion it might also be that DMVs are involved in regulating RNA replication: as long as they are linked to the cytoplasm –as highly bended single membrane vesicles- it would be possible that the DMVs might be the sites of RNA replication, whereas replication would stop upon closure of these vesicles to generate DMVs.

Nevertheless, in the case of coronaviruses [8-10], arteriviruses [11] and HCV [12] the putative single-membrane precursors have so far not been observed. Indeed in the case of HCV the synthesis of RNA correlates in time with the formation of DMVs [12], and in SARS-coronavirus infected cells the bulk of dsRNA, the presumptive RNA replication intermediate, is contained in the inner compartments of interconnected DMVs [8], suggesting that DMVs could be directly involved in replication.

It might also be that these double-membranous structures do not play a direct function on RNA replication or serve some other purpose for the viral replication cycle. Indeed consistent with the membrane topology of the viral proteins involved in replication, the active replication sites of enteroviruses have been allocated to the cytosolic side of these structures [13,14].

Apart from their function, the mechanism of their biogenesis remains also to be completely understood. Their morphological resemblance to autophagosomes, that also have a pair of membranes, might indicate that some of the (+) strand RNA viruses inducing the formation of DMVs might follow a membrane remodeling pathway very similar to the autophagosome formation. That could occur by an already existing cell pathway, usurping for instance the autophagy machinery -or at least some of its components- in order to form these structures.

Future and ongoing investigations will help us to get deeper insights into the biogenesis mechanism, as well as into the function –if any- of these double-membrane viral induced organelles.

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